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Research article

Central venous access devices implantation in children with severe hemophilia a: data from the children comprehensive care center of China

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ABSTRACT

Objectives: To report the perioperative management experience of central venous access devices (CVAD) in Chinese children with severe hemophilia A (SHA) in China.
Methods: This retrospective study included SHA children who underwent Port-A-Cath or peripherally inserted central catheter (PICC) implantation between 2020/01 and 2021/07. Collected data included baseline characteristics, factor replacement regimen and CVAD-related complications.
Results: Nine patients had nine ports placed, and eight patients underwent 10 PICCs placement. Patients without or with low-titer inhibitor (<5 BU) received a port. The median preoperative and postoperative plasma-derived factor VIII (pd-FVIII) doses were 53.0 (44.4–61.1) and 315.9 (88.2–577.8) IU/kg. The median port duration was 189 (15–512) days, with infection incidence of 0.06 per 1000 CVAD days. Patients with high-titer inhibitors (>10 BU) received PICC. The median recombinant factor VIIa (rFVIIa) dose was 87.47 μg/kg before and for 5–7 doses after implantation over 2–3 days. The median PICC duration was 226.5 days, with infection incidence of 0.12 per 1000 catheter-days.
Conclusions: CVADs can be safely implanted in China. PICC implantation is a practical and safe option for SHA children with high-titer inhibitors.

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1. Introduction

Hemophilia A is an X-linked recessive bleeding disorder, based on the residual activity of factor VIII [1, 2]. The global prevalence of Hemophilia A is 17.1 per 100,000 males, and its reported incidence in China is 3.6 per 100,000 males [3]. The severe hemophilia A (SHA) cases are defined as plasma factor VIII activity <1% [1, 4] and require lifelong factor replacement therapy [1]. Implantable central venous access devices (CVADs) have been widely used in the management of hemophilia, including tunneled fully implantable catheters (commonly termed 'ports') and tunneled external silastic catheters [5], with former being reportedly less susceptible to infection and requiring less care [6]. On the other hand, a peripherally inserted central catheter (PICC) is easier to implant and cheaper. Although CVADs are recognized for prophylaxis and immune tolerance therapy (ITI) in young children with hemophilia, the evidence to guide best practices is fragmentary, and standardized methods for CVAD use have yet to be established.

The current recommendations for CVAD in hemophilia recommend preoperative and postoperative factor replacement for patients with inhibitors needing an activated prothrombin complex concentrates (PCC) or recombinant factor VIIa (rFVIIa) [5, 7]. It is estimated that approximately 30% of SHA children treated with prophylaxis and 90% of those on ITI have a CVAD [7]. However, the optimum regimen for the surgical placement of CVAD in SHA children has not yet been established and recommendations vary significantly from one report to another [8]. Few details have been reported regarding factor dosing schedules and acute complications of CVAD insertion and removal in pediatric patients with SHA. Moreover, due to difficult access to factor replacement, in China CVAD procedures in SHA children are rarely carried out and the CVAD implementation status remains unclear.

As a developing country, China is exploring hemophilia care and has already achieved considerable progress in the last decade [3, 9]. Beijing Children's Hospital had carried out the treatment and research of hemophilia in children since 2001, establishing professional outpatient clinics and treatment rooms. In 2010, the comprehensive medical service system for children with hemophilia was improved with the support from the Hemophilia International Project. It is currently the Ministry of Health's training Centre for Children's hemophilia and the National Demonstration Unit for Comprehensive treatment of children's hemophilia. Therefore, this study aimed to report the perioperative management experience of CVAD in Chinese children with SHA at a single center in China, mainly including CVAD options, factor consumption, hospitalization duration, and complications.

2. Materials and methods

2.1. Study design and patients

This retrospective study included patients with SHA who underwent port-a-cath or PICC implantation in our hospital between January 1, 2020, and July 1, 2021. The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (approval number: 2019-k-302). The informed consent was waived by the Committee because of the retrospective nature of the study.

The inclusion criteria were 1) <18 years of age, 2) diagnosis of SHA with the plasma content of coagulation factor activity less than 1%, and 3) >20 exposures to the FVIII containing product (exposure is defined as any 24-hour period in which product is given). The exclusion criteria were 1) active infections, including severe dental caries, 2) arterial or venous thrombosis, or clinical symptoms of thrombophilia, or 3) severe heart, lung, or liver dysfunction or other severe diseases.

The patients were divided by the types of CVAD they received. The patients without inhibitor or with low-titer inhibitor (<5 BU) were implanted with Port-A-Cath, and the others with high-titer inhibitor (>5 BU) underwent PICC insertion.

2.2. CVAD implantation procedures

The first CVAD implantations were performed when the children were hospitalized. A series of examinations was performed to rule out implantation contraindications, including blood routine, liver and kidney function, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) testing, electrocardiogram (ECG), and chest X-ray.

The port-a-caths were implanted according to the anatomical location by the same pediatric surgeon under general anesthesia and using a strict sterile technique. Two brands were used during the study period, including the Port-A-Cath® (Smiths Medical, Lower Pemberton, UK) and the Bard Access Systems (Bard Peripheral Vascular, Inc., Tempe, AZ, USA). The choose of catheter size is due to jugular vein caliber. The right internal jugular vein was selected for incision, and the catheter was placed into the superior vena cava, with the distal catheter tip located in the 6-7th intercostal space. The port was placed and fixed in a subcutaneous pocket. Chest X-ray confirmed the position of the tip postoperatively. Broad-spectrum antibiotic prophylaxis was not given routinely before and after implantation. A well-trained nurse replaced the transparent dressing covering 24 to 48 h later. The catheter was not accessed until the absence of bleeding, swelling, and mechanical problems.

The PICCs were inserted by specially trained nurses in the treatment room. Local anesthesia and sedation were prescribed during PICC insertion. The PICC used was the Groshong® Catheter (NXT single-lumen; Bard Peripheral Vascular, Inc., Tempe, AZ, USA), which was placed in the right or left basilic vein, cephalic vein, or median cubital vein. The blood vessel was punctured under ultrasonographic guidance to minimize vessel damage. PICC lines was placed using ECG to confirm the catheter tip. The insertion region with the PICC was covered with a transparent adhesive dressing using a strict sterile technique and inspected daily. A chest X-ray was used to confirm the catheter tip in the 5-6th intercostal space. The parents had to keep compressing for more than 12 h after the puncture. The venous access was obtained via the PICC catheters after confirmation of the absence of bleeding, swelling, and

mechanical problems. Flushing was done with normal saline alone. The dressing was changed routinely 48 h later, unless the sterile gauze was soaked with blood. The hemostasis protocol was adjusted promptly according to the local swelling and bleeding manifestations of the arm.

2.3. Hemostatic regimen during CVADs implantation

The factor replacement regimen for port implantation depended on the titer of the inhibitor. Children without inhibitors received infusions of plasma-derived factor VIII (pd-FVIII). An infusion of 50 IU/kg factor concentrate was given half an hour before surgery, with the goal factor level of 100%. Then, factor VIII at 30–50 IU/kg was injected over the first 4 h postoperatively, and the same dose was administered over longer time intervals. All doses were rounded to the nearest vial to avoid waste. The administration was gradually prolonged for the next 48 to 96 h. In one patient with low-titer inhibitor and bleeding frequently, perioperative coverage was achieved using rFVIIa. rFVIIa was administered at 90 μg/kg preoperatively and then at 90 μg/kg every 4 h postoperatively for 8 h. Domestic PCC at a dose of 25–50 IU/kg and rFVIIa at the same dose were used alternately over the next 48 to 96 h.

For PICC implantation, rFVIIa was administered to prevent puncture bleeding at a dose of 90 μg/kg i. v. half an hour before PICC implantation. The same dose of rFVIIa was given every 4 h for the first 8 h. After that it was continued at intervals of 6, 8, and 12 h. Alternatively, PCC at a dose of 25–50 IU/kg was administered to lower the cost. Treatment was discontinued if there was no evidence of bleeding.

2.4. Follow-up

Face-to-face comprehensive caregiver education and CVAD user manual were provided 48 h after implantation by the hemophilia care team. The families were instructed to monitor the signs and symptoms of possible CVAD-related complications and contact the treatment center if any problems were experienced. Ports and PICC were flushed after each use by caregivers at home. The catheters were tested at least every month by nurses in a local hospital. A physical examination was performed in our center every 3 months to monitor the signs of infection, thrombosis or device malfunction. To exclude thrombosis, ultrasonography was performed every 6 months. The decision and process of removal were carried out in our center.

2.5. Data collection and definitions

The collected data included patient demographics, the indication for CVAD, type of CVAD, factor coverage during CVADs procedure, level of inhibitor (before insertion, every 3 months and at the end follow-up period), length of hospitalization, acute and extended complications, the period of the catheter indwelling before its removal or the end of the observation period. The data was acquired from the electronic medical records based on the prescribed regimen by the Hemophilia Treatment Center.

Acute complications were defined as events that occurred within the first week after CVAD implantation. Hematoma referred to swelling, bruising, and bleeding around the port-a-cath or PICC sites. Catheter-related infection incidence rates (per 1000 days) were

Table 1
Characteristics of patients and central venous access devices.

Characteristic	CVAD type	
	Port-A-Cath	PICC
Total n of patients	9	8
CVAD placed, n	9	10
Age (years) at first CVAD placement, median (range)	2.83 (0.58–10.33)	1.79 (1.06–2.58)
Weight (kg) at first CVAD placement, median (range)	14.15 (9–42.4)	12.0 (9–14)
Treatment purposes, n (%)		
Prophylaxis	8 (88.9%)	0
ITI	1 (11.1%)	1 (12.5%)
ITI + IS	0	7 (87.5%)
Replacement factor, n (%)		
pd-FVIII	8	2
rFVIIa	0	3
rFVIIa + PCC	1	5
Times of administration, median (range)	7 (5–13)	5.5 (5–7)
Hospitalization days, median (range)	3.67 (3–5)	2.50 (2–3)
CVAD days (d), median (range)	189 (15–512)	226.5 (73–371)
Removal CVAD, n	1	2
Extended complications n of patients	1	6
Hematoma	1	0
catheter-related infection rate per 1000 CVAD days	0.06	0.12
Thrombosis	0	0
Mechanical problem	1	4

CVAD: central venous access devices; PICC: peripherally inserted central catheter; ITI: immune tolerance therapy; IS: immunosuppression; PCC: prothrombin complex concentrates.

Table 2
The scheme of CVAD placement.

Patient no.	Age at insertion (years)	Weight (kg)	Peak historical inhibitor titer (BU/ml)	Pre-CVAD inhibitor titer (BU/ml)	Type of CVAD	Aims	Days in hospital	Replacement therapy	Preop dose (Pd FVIII IU/kg or rFVIIa μg/kg)	Types and dosage of Postop-CVAD	Postop number of doses	Catheter survival (days)	Inhibitor titer at the end follow-up period	Complications	
														Acute	Extended
P1	2.83	17.3	11.4	<0.6	Port-A-Cath	Prophylaxis	3	Pd FVIII	57.8 IU/kg	Pd VIII 88.2 IU/kg	5	511	<0.6	None	None
P2	10.33	42.4	2	<0.6	Port-A-Cath	Prophylaxis	3	Pd FVIII	51.9 IU/kg	Pd VIII 311.3 IU/kg	6	314	<0.6	None	None
P3	1.42	13.1	78.1	<0.6	Port-A-Cath	Prophylaxis	3	Pd FVIII	61.1 IU/kg	Pd VIII 320.6 IU/kg	7	33 Removal	2.2	Restlessness	Infection
P4	0.83	9	<0.6	<0.6	Port-A-Cath	Prophylaxis	5	Pd FVIII	44.4 IU/kg	Pd VIII 577.8 IU/kg	13	279	<0.6	Buckling (Revision)	None
P5	3.75	14.8	68	0.9	Port-A-Cath	Prophylaxis	5	Pd FVIII	54.1 IU/kg	Pd VIII 513.5 IU/kg	10	277	<0.6	None	None
P6	6.08	20	44	<0.6	Port-A-Cath	Prophylaxis	5	Pd FVIII	50.0 IU/kg	Pd VIII 400 IU/kg	8	189	<0.6	None	None
P7	0.58	12	<0.6	<0.6	Port-A-Cath	Prophylaxis	3	Pd FVIII	50.0 IU/kg	Pd VIII 300 IU/kg	6	69	<0.6	Restlessness + fever	None
P8	3.25	14.2	<0.6	<0.6	Port-A-Cath	Prophylaxis	3	Pd FVIII	56.3 IU/kg	Pd VIII 197.2 IU/kg	7	42	<0.6	Restlessness	None
P9	1.50	12	8.8	3.4	Port-A-Cath	ITI	3	rFVIIa + PCC	83.0 μg/kg	rFVIIa 3mg + PCC 1200IU	7	14	3.9	Haematomas	None
P10	1.83	9.3	512	45.1	PICC	ITI + IS	3	rFVIIa + PCC	106.5 μg/kg	rVIIa 5 mg + PCC 600 IU	7	73	161.3	None	Occlusion
P11	1.75	14.1	512	161.3	PICC	ITI + IS	3	rFVIIa + PCC	70.9 μg/kg	rVIIa 5 mg + PCC 300 IU	6	80	71.9	None	Rash/ Infection
P12	1.92	11.9	1024	161.3	PICC	ITI + IS	2	rFVIIa	84.0 μg/kg	rVIIa 5 mg	5	371	6.6	None	Occlusion/ Crack
P13	1.67	12.1	84.5	81.9	PICC	ITI + IS	3	rFVIIa + PCC	82.6 μg/kg	rVIIa 2 mg + PCC 1800 IU	5	224	0.7	None	Crack

(*continued on next page*)

Table 2 (*continued*)

Patient no.	Age at insertion (years)	Weight (kg)	Peak historical inhibitor titer (BU/ml)	Pre-CVAD inhibitor titer (BU/ml)	Type of CVAD	Aims	Days in hospital	Replacement therapy	Preop dose (Pd FVIII IU/kg or rFVIIa μg/kg)	Types and dosage of Postop-CVAD	Postop number of doses	Catheter survival (days)	Inhibitor titer at the end follow-up period	Complications	
														Acute	Extended
P14	1.92	11	25.3	10	PICC	ITI	2	rFVIIa + PCC	90.9 μg/kg	rVIIa 3 mg + PCC 1200 IU	6	229	< 0.6	None	Infection
P15	2.58	14	76.8	76.8	PICC	ITI + IS	3	rFVIIa + PCC	142.9 μg/kg	rVIIa 5 mg + PCC 600 IU	6	279	< 0.6	None	Occlusion
P16	1.25	9	75.5	31	PICC	ITI + IS	2	rFVIIa	111.1 μg/kg	rVIIa 5 mg	5	340	2.6	None	Occlusion/ Crack
P17	1.06	13.1	86.4	78.1	PICC	ITI + IS	2	rFVIIa	76.4 μg/kg	rVIIa 5 mg	5	110	2.2	None	Rash/ Crack

CVAD: central venous access devices; PICC: peripherally inserted central catheter; ITI: immune tolerance therapy.

defined as the number of new infections during the study period divided by the total 'CVAD days' of observation. Infections could occur locally, regionally (tunnel or pocket), or systemically (line sepsis and bacteremia).

2.6. Statistical analysis

Descriptive statistics was performed using SPSS 20.0 (IBM, Armonk, NY, USA). The continuous data were expressed as median (range). Categorical variables were presented as frequency and percentage.

3. Results

3.1. Characteristics of the patients

Patient characteristics are presented summarily in Table 1 and detailed in Table 2. Nine patients had nine ports placed at a median age of 2.83 (range, 0.58 to 10.33) years. The median weight at implantation was 14.2 (range, 9 to 42.4) kg. Five patients in the port implantation group were exposed >150 days, the others <50 days. The primary indications for port-a-cath insertion were prophylactic treatment (n = 8, 88.9%) and ITI (n = 1, 11.1%).

Eight patients underwent the placement of 10 PICCs. At implantation, the median patient age was 1.79 (range, 1.06 to 2.58) years, and the median weight was 12.0 (range, 9–14) kg. The median time from diagnosis to PICC insertion was 11.5 (range, 3 to 19) months and a median of 4.0 months after the development of inhibitor. The main purposes for PICC implantation group were ITI-immunosuppression (n = 7, 87.5%) and ITI therapy (n = 1, 12.5%).

3.2. CVAD implantation

The right internal jugular vein was used for all port insertion cases, with a 100% success rate. The catheter size was 5 Fr in six patients and 6 Fr in three patients. Six ports were accessed within 48 h after the procedure.

The success rate of PICC implantation was 100%. The PICC site was the basilic vein in 40%, the median cubital vein in 20%, and the cephalic vein in 40%. The primary orientation was on the left side. The catheter size most commonly was 3 Fr (90%). The median internal and external catheter lengths to the skin were 21.5 and 5.0 cm, respectively.

3.3. Hemostatic cover regimen

For patients receiving a port-a-cath, seven patients without inhibitor (<0.6 BU) and one case with an inhibitor level of 0.9 BU were treated with pd-FVIII when the ports were implanted. The median preoperative doses of pd-FVIII were 53.0 (range, 44.4 to 61.1) IU/kg. The median postoperative doses were 315.9 (range, 88.2 to 577.8) IU/kg, with 5–13 doses administered. The total doses per surgery day per body weight were 115.1 (range, 39.0 to 127.2) IU. At CVAD insertion, the patients were admitted to the hospital for a median of 3.7 (range, 3 to 5) days. Two patients had low inhibitor titer, at 0.9 BU and 3.4 BU, respectively. The patient with inhibitor at 3.4 BU received 1 mg of rFVIIa preoperatively. rFVIIa and the prothrombin complex were injected alternately every 4 to 6 h over the next 48 h, resulting in a total of seven doses postoperatively. Details are shown in Table 2.

For patients receiving a PICC, there were five (62.5%) patients with inhibitors >64 BU before implantation. The median titer of inhibitors was 77.5 (range, 10.0–161.3) BU. rFVIIa was given at a median dose of 87.5 μg/kg before implantation. Bleeding was well controlled in six patients (75%). The median number of doses after implantation was 5.5 (range, 5 to 7), and the length of treatment was 2 to 3 days. Three patients received rVFIIa alone after insertion, while 62.5% were treated alternatively with rFVIIa and PCC. Details are shown in Table 2.

3.4. Acute and long-term complications

The median port duration was 189 (range, 15 to 512) days. The total duration of PICC was 226.5 (range, 73 to 371) days. In one case, because of the COVID-19 pandemic, the duration was more than one year.

The acute complications that occurred within 72 h after port implantation included one case of fever, three cases of restlessness, one hematoma, and a buckling catheter. The hematoma occurred by accident in the child covered with rFVIIa and within 2 days after surgery. The child received additional factors on postoperative days 4–6. The buckling catheter was revised by another surgery and additional three factor replacements. Acute local bleeding from PICC placement was treated by appropriate factor replacement and local compression. No severe bleeding occurred.

The long-term complications included catheter-related infections and mechanical problems. No thrombosis was documented. One port-related infection was documented during the study and accounted for 0.06 infections per 1000 CVAD days [confidence interval (CI) 0.01–0.10]. A fever and purulent secretions were observed in association with two PICC catheters, evaluated as 0.12 infections per 1000 CVAD days [confidence interval (CI) 0.10–0.13]. All infections were treated with antibiotics. The infectious port was removed 33 days after implantation, while the PICCs were kept after antimicrobial therapy. Four of the 10 PICCs had obstruction issues, all successfully managed using urokinase solution for several hours. Rashes repeatedly occurred around the catheter in 25% of the PICC patients, which were improved by frequently replacing the dressing. Connection cracking at the interface of the catheter occurred in four PICC patients, and the external catheter was shorted to replace the connection and to keep it operational.

Table 3
Literatures of describing perioperative management of CVAD placement in patients with hemophilia A.

Study	Years	Number of patients	Median age (month) (range)	Treatment days for surgery (range)	Therapeutic regimen for surgery	Preop factor dosing (range)	Postop factor dosing (range)	duration of CVAD (days)	CVADs related bleeding episodes	Infection rate (per 1000 catheter -days)
Bollard et al. [18]	1988 to 1998	13HA (5 with inhibitor)	4–156	3–5	FVIII (pd factor VIII or rFVIIIa): Preop: 50–100 IU kg^{-1} Postop: >75% level for 3–5 days FEIBA for inhibitors: Preop: 100 U kg^{-1} Postop: 50 U kg^{-1} Q12h	-	-	695 (120–2145)	17%	3.4
Santagostino et al. [19]	1997 to 1998	15HA (2 with inhibitor)	66 (1.2–118.8)	6.0	rFVIII: Preop: 70–100 IU kg^{-1} Q12h > 80% Postop: 50–80 IU kg^{-1} Qd >50% level for 1–6 days rFVIIa for inhibitors: Preop: 120 μg kg^{-1} Postop:16.5 μg kg^{-1} Q1h or 90 μg kg^{-1} Q2-3h for 24h Q4-6h for 5 days	142% (86–211) %	80 (50–100) IU $kg^{-1}d^{-1}$	413 (125–509)	1/15	0.33
O'Connell et al. [20]	1995 to 2000	12 HA (12 with inhibitor)	1–16 y	0.5–3	rFVIIa: 90 μg kg^{-1} Q2h for the first 24h, then 90 μg kg^{-1} Q4h for the next 24h or Q3h for 24h, Q4h for the another 24h	-	43.2mg (19.2–124.8)	-	2/12	-
Titapiwatanakun et al. [21]	1995 to 2007	15HA (4 with inhibitor)	14 (0.7–144)	5–7	FVIII: Preop: level at 100% Postop: ≥50% level for 48 h, then twice daily for 5–7 days	-	-	1361 (2–2420)	None	0.22
Harroche et al. [22]	1995 to 2010	49HA (38with inhibitor)	31 (3–128)	4–5	FVIII infused tid per day and rFVIIa Q2h then was gradually reduced	-	-	1269 (113–2794)	9/50	0.0578
Fonseca et al. [15]	2004 to 2010	15 HA	25 (10.8–73.2)	5.7 (3–8)	rFVIII: Preop: 75 IU kg^{-1} (1-3times to level of 100%) Postop: Q8h ≥ 50% level for 72 h, then 50 IU kg^{-1} Q12 h for 1days, 75 IU kg^{-1} Qd for 1–3days	93.5 IU kg^{-1} (53.7–145.4)	818.7 IU kg^{-1} (441–1258)	N/A	None	None
Shibata et al. [25]	2006 to 2010	4 HA (3 with inhibitors)	55.5	5	FVIII: Preop: at level of 100% Postop: 50% level for two days and then 20% level for 3–5days	-	(5–22.2) IU $kg^{-1}h^{-1}$	-	-	-
Bedoya et al. [28]	2006 to 2016	15HA (15 HA; 13 with inhibitors)	46.8 (8.4–272.4)	5	FVIII: Preop: FVIII level at 100% Postop: ≥50% level for 48 h, then >25% level for 72h	-	-	465 (10–2992)	5/18	0.57
Minna et al. [16]	2000 to 2018	34 HA	13.8 (3.8–36.2)	4 (1–4)	rFVIII: 271 IU kg^{-1} (23–1025)	-	-	-	1/34	-

(*continued on next page*)

Table 3 (*continued*)

Study	Years	Number of patients	Median age (month) (range)	Treatment days for surgery (range)	Therapeutic regimen for surgery	Preop factor dosing (range)	Postop factor dosing (range)	duration of CVAD (days)	CVADs related bleeding episodes	Infection rate (per 1000 catheter -days)
Minna et al. [16]	2000 to 2018	110HA	15 (0.5–53.8)	6 (5–7)	rFVIII: 678 IU kg-^{1} (598–1368)	-	-	-	1/110	-
Bensadok et al. [26]	2006 to 2019	14HA (2 with inhibitors)	11 (8–34)	1–2	FVIII: Preop: 50 IU kg^{-1} Postop: 50 IU kg^{-1} Q8-12h for 24 to 48 h rFVIIa or aPCC for inhibitors: Preop: rFVIIa 270 μg kg^{-1} or aPCC 100 UI kg^{-1} Postop: same dose Q8-12h for 24 to 48 h	-	-	799 (123–1568)	None	0.12

CVAD: central venous access device; HA: hemophilia A; FEIBA: Factor eight inhibitor bypassing activity.

3.5. Follow-up and ITI effectiveness in PICC patients

PICCs were removed in two cases, one due to accidental self-removal and the other because of the longevity of up to 1 year. In both cases, the PICCs were replaced in the outpatient clinic at the time of the lowest titer of inhibitor. Before and after the placement, they were given pd-FVIII. No bleeding occurred. During follow-up, all PICC patients were treated with ITI, and no cases gave up. In six patients using PICC, the inhibitors levels turned negative and lower than 10 BU at the end of follow-up.

4. Discussion

CVADs are of recognized value for young children with hemophilia, but evidence to guide best practices has been fragmentary, especially in developing countries. This study aimed to report the perioperative management experience of CVAD in Chinese children with SHA at a single center in China. The results suggest that CVADs can be safely implanted in China. PICC implantation is a practical and safe option for children with hemophilia A and high-titer inhibitors. The pre/post-implantation bypassing replacement regimen and CVAD management monitor is critical.

The choice of the most suitable CAVD should be carried out on an individual basis, after assessment of the benefits and risks. The final decision of CVAD choice should consider factors such as the caregiver/patient preference, the medical goal, age at implantation, expected risk of complications, bleeding frequency, and healthcare costs. Fully implantable devices and external catheters have potential advantages and disadvantages, and are suitable for different purposes [10]. As previously reported, ports are commonly preferred to external catheters due to less susceptibility to infections, longer duration, less care required, and little effect on exercise [6]. Ports are more suitable for children younger than 2 years old because the catheters implanted subcutaneously are not easy to be removed accidently [11]. Prophylaxis CVAD can be implanted for a longer duration to achieve a gradual transition to self-injection, while port provides a stable, long-term catheter with a low incidence of infection and minimal impact on activity in pediatric patients. This choice might be more suitable for young patients without inhibitor or with low-titer inhibitor at the condition of adequate replacement. On the other hand, external catheters are user-friendly and less expensive, easily inserted and removed without surgery and do not require a needle stick. Patients with inhibitors had to face frequent and uncontrolled bleeding and economic burden; under these circumstances PICCs may cost less for patients with high-titer inhibitor. It can be used at any time, which is right for frequent injection of ITI treatment and timely treatment of bleeding, and can be removed or replaced with Port when achieving a negative inhibitor titer. Considering the practical situation of pediatric patients with SHA discussed above, in this study Port-A-Cath was chosen for patients without inhibitor or with low-titer inhibitor (<5 BU) and PICC for patients with high-titer inhibitor (>10 BU).

Surgical treatment is comparatively safe for patients with hemophilia A under the conditions of adequate clotting factor concentrate (CFC) prophylaxis. The recommendations for CVAD in patients with hemophilia were previously described [5, 7]. Still, factor administration varied individually among the reports, as reviewed by Neunert et al. [8]. Other studies demonstrated the safety and efficacy of lower doses of the CFCs for surgical prophylaxis and explored replacement schedules for different types of surgical procedures [12, 13]. As previously reported, the duration of hospitalization is variable, ranging from 24 h to 14 days [8]. The incidence of postoperative hemorrhage was overall calculated as 11% [8], and there is no evidence that higher levels of factors reduce the incidence of postoperative bleeding. In addition, the peak treatment moment is associated with up to a 60% increase risk of inhibitor development in adult patients with hemophilia A [14]. However, there is a limited number of published studies reporting the management of CVAD insertions in children. The experience of the McMaster Children's Hospital showed that the dose of factor administration had gradually decreased over time and that the total perioperative dose was 912.2 IU/kg [15]. Minna et al. [16] proposed that less than 4 days may be as safe and effective as longer replacement therapy. We analyzed regimens of factor administration from the literature over the last two decades [11, 12, 13, 14, 17, 18, 19, 20, 21, 22] and found that the dosage of factor had gradually reduced and length of hospital stay had shortened (Table 3). Of note, these studies are mostly about CVADs in general, and few of them make the distinction between ports and PICC. Therefore, these studies performed in Western settings suggest that decreasing the dosage and shortening hospitalization do not compromise the safety of CAVD implantation.

In China, factor is difficult to obtain and expensive. Therefore, low-dose prophylaxis in pediatric hemophilia A has proved to be effective in reducing bleeding rates and improving quality of life [23, 24]. This study demonstrated that it might be feasible to use much lower dosages of factors than the recommended levels for children with SHA without inhibitor or with low-titer inhibitor when implanting a Port-A-Cath. We found that only one preoperative dose half an hour before the surgery could ensure the safety of the procedure. The median postoperative doses were 315.9 (range, 88.2 to 577.8) IU/kg, with the 5 to 13 doses. The median treatment days for CVAD surgery were 3.67 (range, 3 to 5). The total consumption of dose per surgery day per body weight was 115.1 (range, 39.0 to 127.2) IU. The variation on postoperative frequency and administration depended on age, activity, and additional surgery.

There were little data on administration replacement protocols and acute perioperative complications in patients with high titer inhibitors, and few details about PICC placement are available in the literature. Shibata et al. [25] used high-dose FVIII concentrates in four hemophilia A patients with inhibitors and got reliable hemostatic control and successfully prevented intra- and postoperative hemorrhage; they infused FVIII to obtain circulating FVIII:C to be 100% preoperatively, and continuous infusion to maintain the levels of FVIII:C above 50% for 2 days after surgery, and above 20% for an additional 3 to 5 days. O'Connell et al. [20] administered rFVIIa to prevent surgical bleeding of CVAD; the median duration of treatment was 48 h, and the median total dose was 43 (range, 19 to 125) mg. One study reported two patients with peak titer >10 BU who received 270 μg/kg of rFVIIa and/or 100 IU/kg of aPCC, then received a second peripheral vein infusion 8–12 h later [26]. Further investigation in China about low-dose ITI strategy to HA children with high-titer inhibitor showed a relatively satisfactory success rate and economic advantages [27]. There are no pediatric data to investigate dosing and duration of treatment during PICC implantation in patients with high titer inhibitors. This study reported that

the median level of inhibitor before PICC implantation was 77.45 BU. The median pre-procedure dose of rFVIIa for prevention of bleeding was 87.47 μg/kg, and three patients received rVFIIa post-procedure, while five patients were treated alternatively with rVFIIa and PCC. The bypassing therapy was mostly given 5–7 doses for 2–3 days. The total dose of rFVIIa was less than that reported previously. Alternating rVFIIa and PCC appears to be safe, and such a strategy could be more economically suitable for developing countries.

CVADs are widely used in children with hemophilia A, but the occurrence of complications, such as infection and thrombosis, limits CAVD survival. There were few reports of thrombosis despite long-time follow-up, while infections were commonly reported [5, 18, 19, 21, 22, 26, 28], where infectious and thrombotic complications accounted for CVAD removal in 70% and 4% of the cases, respectively.[29] In the present study, three of 17 patients (17.6%) had infections, and no thrombosis was observed.

The previously reported factors associated with an increased risk of infection include the presence of inhibitors, use of external catheters, and age between 2 and 6 years at the time of CVAD placement [29]. Port may have a notably lower risk of infections compared to external catheters. The complication rate of PICC in our cohort was lower than that reported in the literature: two cases of infection occurred locally, and the catheters were not removed. Aseptic techniques, longer follow-up and additional education of caregivers might help in reducing the risk of infection.

The International ITI study showed lower success rates, higher failure rates, and slower ITI responses in patients with infected CVAD, suggesting that catheter-related infections may impact ITI outcomes [5], and highlighting the importance of aseptic techniques. During the follow-up period all patients with PICC were treated with ITI, and no patients decided to terminate the treatment. The levels of inhibitors turned negative in 75% of patients. It suggests that PICC placement plays a positive role in the progress of ITI and a longer follow-up time is needed to observe the complications.

There were some limitations to this study. The sample was relatively small and from a single center, with no control group to observe perioperative CVAD management experience. The choice of CVAD was based on many additional factors such as the caregiver/patient preference, the medical goal, age at implantation, expected risk of complications, bleeding frequency, and healthcare costs, which may have led to additional bias. Moreover, there was variability in the replacement schemes due to individual differences. The process of insertion depended on the high experience of the surgeon and specialist nurses. Evidence-based practice guidelines for perioperative strategy in patients with hemophilia are not available.

5. Conclusion

CVADs were effective in children with SHA who need long-term venous access for Factor replacement therapy, with a low rate of serious complications. This study reported a single-center experience on CVAD implantation in children with hemophilia A in China. The results suggest that CVAD can be safely implanted with relative low doses of factors and short hospital stay. In addition, PICC implantation is a feasible and safe option for SHA children with high-titer inhibitor for ITI treatment. The pre/post bypassing replacement regimen and CVAD management monitor might help.

Author contribution statement

Runhui Wu conceived and designed the experiments; All authors (Qian Xu, Chunli Wang, Wei Cheng, Yingzi Zhen, Yaguang Ding, Guoqing Liu, Wanru Yao, Zhenping Chen, Zhiqiang Li, Runhui Wu) performed the experiments; Qian Xu, Chunli Wang and Wei Cheng analyzed and interpreted the data; Guoqing Liu, Chunli Wang and Wei Cheng contributed reagents, materials, analysis tools.

Qian Xu wrote the paper; All authors (Qian Xu, Chunli Wang, Wei Cheng, Yingzi Zhen, Yaguang Ding, Guoqing Liu, Wanru Yao, Zhenping Chen, Zhiqiang Li, Runhui Wu) approved the version submitted.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declares that there is no conflict of interest.

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